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EXAMINER	
CLARK, GREGORY D	

ART UNIT	PAPER NUMBER
1786	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/561,774	BORCK ET AL.	
	Examiner	Art Unit	
	GREGORY CLARK	1786	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-21 and 24-27* is/are pending in the application.

4a) Of the above claim(s) *2,8,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-21 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges the receipt of the applicant's arguments/remarks, and amended claims dated 03/01/2010. Claims 1, 3-7, 9-21 and 24-27 are pending

Rejections and objections made in previous office action that do not appear below have been overcome by applicant's amendments and therefore the arguments pertaining to these rejections/objections will not be addressed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. **Claims 1, 3-7, 9-20 and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliot (US 2003/0236567) in view Collombel (US 5,166,187) and Kuo (US 6,537,979).**

2. **Regarding Claims 1,** Elliot teaches an implantable prosthesis which may be used as a graft to replace a portion of a bodily passageway (e.g., vascular graft), or may be used within a bodily passageway such as an endovascular stent-graft (paragraph 20). The implantable stent formed can be made of a metal, such as stainless steel, tantalum, or niobium (paragraph 22). Elliot teaches that the skirt (outer covering the

prosthesis) can be coated with materials that are susceptible to cell ingrowth (tissue simulating, biocompatible) (paragraph 25) and that one or more skirts (partial areas or partial layers) can be provided to form seal along various points about the prosthesis (paragraph 26). These materials include: collagen, fibrin, hyaluronic acid, chitosan, and/or other polysaccharide (paragraph 25). Elliot does not teach a coating composition where the vivo degradation of the polysaccharide layer is slowed from the outside in the direction of the main body of the implant or where a single layer is composed of hyaluronic acid and chitosan.

Collombel teaches that chitosan can be used to coat prostheses (column 14, lines 2-5) and the speed of the enzymatic degradation of chitosan is a function both of its molecular weight and its degree of acetylation (Column 5, lines 64-66).

Kuo discloses a number of approaches to modifying hyaluronic acid to reduce (control) the diffusivity (degradation) in vivo one of which includes the use of crosslinking agents (column 2, lines 19-23). Some crosslinking agents disclosed by Kuo include formaldehyde, divinyl sulfone and bis-epoxides (column 3, lines 24-42) and carbodiimide (column 3, line 15-17). Kuo also discloses that by choosing the concentration of hyaluronic acid one can control the rate of degradation or diffusion (column 12, lines 43-44).

Elliot teaches an implantable prosthesis which can be composed of hyaluronic acid and chitosan. Collombel and Kuo teach that both hyaluronic acid and chitosan can be selected with the appropriate structural features (acetylation in chitosan and crosslinking in hyaluronic acid) to control the degree of degradation in a given region.

In addition, the simple crosslinking of hyaluronic acid and acetylation of chitosan is achieved by a well known reaction procedures. Moreover, the blocking of reactive organic groups such as the carboxylic acid group or the hydroxyl group is a well known method to decrease the reactivity of an organic material to a given medium. To control the degradation rate a person skilled in the art would conduct routine experiments to ensure that a suitable percentage of reactive organic groups were blocked to control the degradation rate.

Collombel and Kuo teaches the very structural features (acetylation of chitosan and hyaluronic acid modified with crosslinking agents) and molecular weight requirements necessary for a person of ordinary skill in the art at the time of the invention to formulate prosthetic coatings with a controlled degradation rate in a given region.

The process would involve ensuring that through routine experimentation that the chitosan on the external portion of the coating structure has a sufficient molecular weight and a suitable level of acetlylation to slow the polysaccharide degradation by a desired amount for the intended application. Likewise, ensuring that through routine experimentation that the concentration of crosslinked hyaluronic acid on the external portion of the coating structure was of a suitable level to slow the polysaccharide degradation by a desired amount for the intended application.

With a reasonable expectation of success, a person of ordinary skill in the art with the teachings of Collombel and Kuo would modify the chitosan and hyaluronic acid

of Elliot with the acetylated chitosan of Collombel and the crosslinked hyaluronic acid of Kuo in order control the rate of degradation.

The motivation for combining the references would have been to utilize known techniques to control the degradation rates of chitosan and hyaluronic acid on coated implants to improve compatibility with surrounding tissue and decrease the likelihood of infection.

Elliot discloses that hyaluronic acid and chitosan can be used as biodegradable coating materials for implants. The simple combining or two polysaccharide materials (to form a single layer) for which the cited reference teaches utility as implant coating materials is not considered as patentable subject matter.

3. **Regarding Claim 3,** Elliot teaches an implantable prosthesis that can be made from materials that include: collagen, fibrin, hyaluronic acid, chitosan, and/or other polysaccharide materials (paragraph 25).

As Elliot uses a like material (chitosan) in a like manner as claimed, it would be expected that the prosthesis (implant) would have the same characteristics claimed, particularly the adhesion properties, absence a showing of unexpected results.

4. **Regarding Claim 4,** Elliot teaches an implantable prosthesis that can be made from materials that include: collagen, fibrin, hyaluronic acid, chitosan, and/or other polysaccharide (paragraph 25). The applicant claims a thickness of 1 to 50 microns. Elliot does not teach the thickness of the chitosan layer.

With a reasonable expectation of successful results, it would have been obvious to one having ordinary skill in the art at the time of the invention to adjust the thickness for the chitosan layer to ensure that a sufficient amount of the adhesive layer was present to avoid slippage of the implanted prosthesis. Such routine experimental would have resulted in a thickness range that covers the ranges in the instant claim.

5. **Regarding 5,** Elliot teaches that the skirt (outer covering the prosthesis) can be coated with materials that include: collagen, fibrin, hyaluronic acid, chitosan, and/or other polysaccharide (paragraph 25). The applicant teaches a total weight of polysaccharide of not more than 50% weight. Elliot does not teach a weight percent for the polysaccharide layer.

With the reasonable expectation of success, it would have been obvious to one having ordinary skill in the art at the time of the invention to add a sufficient amount of polysaccharide material for adequate coverage of the prosthesis. Such routine experimentation to determine the appropriate amount would result in a polysaccharide level that overlaps with the applicant.

6. **Regarding Claims 6 and 7,** Elliot teaches an implantable prosthesis which may be used as a graft to replace a portion of a bodily passageway (e.g., vascular graft), or may be used within a bodily passageway to maintain patency thereof, such as an endovascular stent-graft (paragraph 20). These materials include: collagen, fibrin, hyaluronic acid, chitosan, and/or other polysaccharide (paragraph 25). Elliot does not

teach an average molecular weight of the hyaluronic acid or hyaluronic acid derivative between 300,000 and 500,000 Dalton or between 380,000 and 420,000 Dalton at claimed by the applicant.

With the reasonable expectation of success, a person of ordinary skills in the art at the time of the invention through routine experimentation would adjust the molecular weight of hyaluronic acid or its derivatives based on the amount of durability required for that component. Hyaluronic acid or its derivatives with higher molecular weights would be expected to be more durable than hyaluronic species with lower molecular weights. The determination of the appropriate average molecular weight would overlap with the ranges taught by the applicant in the course of optimization.

7. **Regarding Claims 9 and 11,** Elliot does not teach that the internal area of the polysaccharide layer is not degradable, at least completely within two years or the external polysaccharide layer is degradable with in 100 days as claimed by the applicant.

Kuo discloses that the literature describes a number of approaches to modifying hyaluronic acid to reduce (control) the diffusivity (degradation) in vivo one of which includes the use of crosslinking agents (column 2, lines 19-23). Some crosslinking agents include formaldehyde, divinyl sulfone and bis-epoxides (column 3, lines 24-42) and carbodiimide (column 3, line 15-17). Kuo also discloses that by choosing the concentration of hyaluronic acid one can control the rate of degradation or diffusion (column 12, lines 43-44).

Collombel teaches the usage of chitosan in a biomaterial application where the speed of enzymatic degradation of chitosan is a function both of its molecular weight and its degree of acetylation (Column 5, lines 64-66).

Whereas, Elliot teaches an implantable prosthesis which can be composed of hyaluronic acid and chitosan. Collombel and Kuo teach that both hyaluronic acid and chitosan can be selected with the appropriate structural features (acetylation in chitosan and crosslinking in hyaluronic acid) to control the degree of degradation.

It would have been obvious to a person of ordinary skill in the art at the time of the invention to combine the biocompatible hyaluronic acid and chitosan implantable prosthesis coating taught by Elliot with the suitable structural features (crosslinking in hyaluronic acid and acetylation in chitosan) taught by Collombel and Kuo to give the desired degradation properties in the respective layers to improve tissue compatibility and the decrease the likelihood of infection.

8. **Regarding Claims 10 and 12,** Elliot, Kuo, and Collombel do not teach a an internal of polysaccharide layer thickness of 3 to 50 microns or an external thickness of 10 to 250 microns as claimed by the applicant. Elliot does not teach the thickness of the polysaccharide layer.

With a reasonable expectation of successful results, it would have been obvious to one having ordinary skill in the art at the time of the invention to adjust the internal and the external thicknesses for the polysaccharide layers through routine

experimentation of implant coating levels to determine the appropriate amount which would include the ranges claimed by the applicant.

9. **Regarding Claims 13, 14, 16,** Elliot teaches that the skirt (outer covering the prosthesis) can be coated with materials that are susceptible to cell ingrowth (tissue simulating) (paragraph 25) and the one or more skirts (partial areas or partial layers) can be provided to form seal along various points about the prosthesis (paragraph 26). These materials include: collagen, fibrin, hyaluronic acid, chitosan, and/or other polysaccharide (paragraph 25). Elliot, Kuo, and Collombel do not teach a composition such the vivo degradation of the polysaccharide layer is slowed from the outside in the direction of the main body of the implant, an internal polysaccharide layer that degrades not more than 20% weight within two years or an external polysaccharide layer that degrades at least 50% by weight with in 100 days as claimed by the applicant.

Collombel teaches the usage of chitosan in a biomaterial application where the speed of enzymatic degradation of chitosan is a function both of its molecular weight and its degree of acetylation (Column 5, lines 64-66).

Kuo discloses that the literature describes a number of approaches to modifying hyaluronic acid to reduce (control) the diffusivity (degradation) in vivo one of which includes the use of crosslinking agents (column 2, lines 19-23). Some crosslinking agents include formaldehyde, divinyl sulfone and bis-epoxides (column 3, lines 24-42) and carbodiimide (column 3, line 15-17). Kuo also discloses that by choosing the

concentration of hyaluronic acid one can control the rate of degradation or diffusion (column 12, lines 43-44).

Whereas, Elliot teaches a biocompatible coating for implantable prosthesis which can be composed of hyaluronic acid and chitosan. Collombel and Kuo teach that both hyaluronic acid and chitosan can be selected with the appropriate structural features (crosslinking in hyaluronic acid and acetylation in chitosan) to control the degree of degradation.

It would have been obvious to some of ordinary skill in the art at the time of the invention to combine the biocompatible hyaluronic acid and chitosan implantable prosthesis coating taught by Elliot with the suitable structural features (crosslinking in hyaluronic acid and acetylation in chitosan) taught by Kuo and Collombel to give the desired degradation properties in the respective layers.

The process would involve ensuring that through routine experimentation the materials in the external and internal regions have a sufficient molecular weight and a suitable level of acetylation with respect to the chitosan material based on the teachings of Collombel and the appropriate concentration of crosslinked hyaluronic acid material based on the teachings of Kuo to achieve the desire degradation rate in the internal and external regions. Through such routine experimentation, a person of ordinary skill in the art at the time of the invention could achieve a degradation that is slowed from the outside direction of the main body of the implant, an internal polysaccharide layer that degrades not more than 20% weight within two years or an

external polysaccharide layer that degrades at least 50% by weight with in 100 days as claimed by the applicant.

10. **Regarding Claim 15, 17-19,** Elliot, Kuo and Collombel do not teach the thickness of the polysaccharide layer as be 3 to 50 microns for the internal layer, 10 to 250 microns for the external layer, 10 to 400 microns or 50-120 microns in thickness.

With a reasonable expectation of successful results, it would have been obvious to one having ordinary skill in the art at the time of the invention to adjust the internal and the external thicknesses for the polysaccharide layers with respect to the desired degradation rate through routine experimentation of implant coating levels to determine the appropriate amount for proper surface coverage which would include the ranges claimed by the applicant. In the course of determining the optimal thickness the ranges covered by the applicant would be in scope, absence unexpected results.

11. **Regarding Claim 20,** Elliot teaches the use of hyaluronic acid, chitosan, and/or other polysaccharide as coatings for implantable prostheses. Elliot, Kuo and Collombel do not teach that hyaluronic acid or it derivatives and chitosan are components of a polysaccharide layer as individual substances, copolymers, block polymers made of hyaluronic acid or it derivatives and chitosan or in the form of mixtures.

Elliot, Kuo and Collombel all disclose that hyaluronic acid and chitosan can be used as biodegradable coating materials for implants. The simple combining or two polysaccharide materials for which the cited references clearly reads upon is not

considered as patentable subject matter. In addition, the simply transesterification of hyaluronic acid and chitosan is achieved by a well known condensation polymerization and the use copolymers which result as implant coatings is not considered as patentable subject matter.

12. **Regarding Claims 24 and 25**, Elliot teaches an implantable prosthesis which may be used as a graft to replace a portion of a bodily passageway (e.g., vascular graft), or may be used within a bodily such as an endovascular stent-graft (paragraph 20). Elliot also teaches that the skirt (outer covering the prosthesis) can be coated with materials that are susceptible to cell ingrowth (tissue simulating) (paragraph 25). These materials include: collagen, fibrin, hyaluronic acid, chitosan, and/or other polysaccharide (paragraph 25).

13. **Regarding Claim 26,** Elliot in view Collombel and Kuo teach the invention of claim 1.

Collombel and Kuo teaches the very structural features (acetylation of chitosan and hyaluronic acid modified with crosslinking agents) and molecular weight requirements necessary for a person of ordinary skill in the art at the time of the invention to formulate prosthetic coatings with a controlled degradation rate in a given region as discussed in section 2.

The process would involve ensuring that through routine experimentation that the chitosan on the outer portion of the coating structure has a sufficient molecular weight

and a suitable level of acetylation to slow the polysaccharide degradation by a desired amount for the intended application. Likewise, ensuring that through routine experimentation that the concentration of crosslinked hyaluronic acid on the external portion of the coating structure was of a suitable level to slow the polysaccharide degradation by a desired amount for the intended application.

With a reasonable expectation of success, a person of ordinary skill in the art at the time of the invention with the teachings of Collombel and Kuo would modify the chitosan and hyaluronic acid of Elliot with the acetylated chitosan of Collombel and the crosslinked hyaluronic acid of Kuo in order to achieve a steady rate of degradation of the outer polysaccharide layer.

The motivation for combining the references would have been to utilize known techniques to control the degradation rates of chitosan and hyaluronic acid on coated implants to improve compatibility with surrounding tissue and decrease the likelihood of infection.

14. **Regarding Claim 27,** Elliot in view Collombel and Kuo teach the invention of claim 1.

Elliot teaches that the skirt (outer covering the prosthesis) can be coated with materials that are susceptible to cell ingrowth (tissue simulating, biocompatible) (paragraph 25) and that one or more skirts (partial areas or partial layers) can be provided to form a seal along various points about the prosthesis (paragraph 26).

The examiner interprets "one or more skirts" by in scope with at lest two partial layers can be applied to the prosthesis.

Collombel and Kuo teaches the very structural features (acetylation of chitosan and hyaluronic acid modified with crosslinking agents) and molecular weight requirements necessary for a person of ordinary skill in the art at the time of the invention to formulate prosthetic coatings with a controlled degradation rate in a given region as discussed in section 2.

As Elliot teaches the application of partial layers and Collombel/Kuo teaches the means to control degradation of a polysaccharide layer, It would have been obvious to a person of ordinary skill in the art at the time of the invention to have adjusted the acetylation of chitosan or the modification of hyaluronic acid with crosslinking agents to achieve a desirable degradation in a given layer which would have included layers have different degradation rates, absent unexpected results.

15. **Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elliot (2003/0236567) in view of Collombel (5,166,187) in further view of Kuo (US 6,537,979) and Swan (5,563,056).**

16. **Regarding Claim 21**, Elliot, Collombel and Kuo do not teach the polysaccharide is immobilized covalently or through physisorption on the surface of the implant as claimed by the applicant.

Swan teaches a chemical specie can be immobilized in a three dimensional, crosslinked matrix by bringing together in covalent bonding proximity a desired chemical specie and a polymeric coupling compound such as a photoderivatized polymer having at least two latent photochemical reactive groups per molecule, each latent reactive group being capable when activated of covalently bonding to another coupling compound molecule or to the chemical specie (abstract). Swan also teaches such materials which are readily coupled (immobilized) to a surface include oligomers, homopolymers and copolymers resulting from addition or condensation polymerization, and natural polymers including nucleic acids, oligosaccharides, linear polysaccharides such as amylose, dextran, chitosan, heparin and hyaluronic acid, and branched polysaccharides such as amylopectin, glycogen and hemi-celluloses (Column 3, lines 54-63). Swan also teaches that the immobilization of chemical species (on the surfaces of prostheses that are to be implanted within the body) with growth factors or similar chemical species may contribute to the rapid proliferation of tissue (biocompatibility/ tissue growth) on the prosthesis (Column 1, lines 21-25).

Whereas both chitosan and hyaluronic acid homopolymers and copolymers can be immobilized on a surface covalently it would have been obvious to someone of ordinary skill in the art at the time of the invention to combine the metallic implant coatings taught by Elliot with the immobilization technique taught by Swan to improve biocompatibility/ tissue growth, absent of unexpected results.

17. **Claims 1, 3-7, 9-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wironen (6,685,626) and Collombel (5,166,187) in view of Kuo (US 6,537,979).**

18. **Regarding Claim 1,** Wironen teaches a biocompatible *(*Column 5, lines 43-45*)* coating (called by the term "a carrier", Column 4, lines 14-20) system for metallic implants (Column 4, lines 30-35). The carrier coating selected from or may be a combination of materials selected from the following non-exclusive list: collagen; gelatin; carboxymethyl cellulose; hyaluronic acid; polyvinyl alcohol; thrombin; fibrin; albumin; and mucoadhesive polysaccharides such as chitosan, polyalcohols, polyamines, polyvinyls, polyamides and polyesters (Column 5, lines 9-17). *).* The carrier coating is selected from or may be a combination of materials which include hyaluronic acid and chitosan (Column 5, lines 9-17).

Wironen teaches a combination of materials can be used in a single polysaccharide coating layer which reads on the instant "a polysaccharide layer made of chitosan and hyaluronic acid/ hyaluronic acid derivative".

Wironen does not teach a composition such the vivo degradation of the polysaccharide layer is slowed from the outside in the direction of the main body of the implant.

Collombel teaches chitosan is used coat prostheses (column 14, lines 2-5) and the speed of enzymatic degradation of chitosan is a function both of its molecular weight and its degree of acetylation (Column 5, lines 64-66).

Kuo discloses that the literature describes a number of approaches to modifying hyaluronic acid to reduce (control) the diffusivity (degradation) in vivo one of which includes the use of crosslinking agents (column 2, lines 19-23). Some crosslinking agents include formaldehyde, divinyl sulfone and bis-epoxides (column 3, lines 24-42) and carbodiimide (column 3, line 15-17). Kuo also discloses that by choosing the concentration of hyaluronic acid one can control the rate of degradation or diffusion (column 12, lines 43-44).

Whereas, Wironen teaches an implantable prosthesis which can be composed of hyaluronic acid and chitosan. Collombel and Kuo teach that both hyaluronic acid and chitosan can be selected with the appropriate structural features (acetylation of chitosan and hyaluronic acid modified with crosslinking agents) to control the degree of degradation in a given region.

In addition, the crosslinking of hyaluronic acid and acetylation of chitosan is achieved by a well known condensation reaction procedures. Moreover, the blocking of reactive organic groups such as the carboxylic acid group or the hydroxyl group is a well known method to decrease the reactivity of an organic material to a given medium. To control the degradation rate a person skilled in the art would conduct routine experiments to ensure that a suitable percentage of reactive organic groups were blocked to control the degradation rate.

Collombel and Kuo teaches the very structural feature requirements necessary for a person of ordinary skill in the art at the time of the invention to formulate a prosthetic coating with a controlled degradation rate in a given region.

The process would involve ensuring through routine experimentation that the chitosan on the external portion of the coating structure has a sufficient molecular weight and a suitable level of acetlylation to slow the polysaccharide degradation by a desired amount for the intended application. Likewise, ensuring through routine experimentation that a suitable concentration of crosslinked hyaluronic acid on the external portion of the coating structure to slow the polysaccharide degradation by a desired amount for the intended application.

With a reasonable expectation of success, a person of ordinary skill in the art with the teachings of Wironen, Collombel and Kuo would modify the chitosan and the hyaluronic acid of Wironen with the acetylated chitosan of Collombel and the crosslinked hyaluronic acid of Kuo in order control the rate of degradation.

The motivation for combining the references would have been to utilize known techniques to control the degradation rates of chitosan and hyaluronic acid on coated implants to improve compatibility with surrounding tissue and decrease the likelihood of infection.

19. **Regarding Claims *3,*** Wironen teaches the usage of a mucoadhesive polysaccharide layer which contains chitosan (Column 5, lines 14 and 15).

20. **Regarding Claim 4,** Wironen teaches the usage o*f a* mucoadhesive polysaccharide *l*ayer which contains chitosa*n* (Column 5, lines 14 and 15). The adhesion-promoting material is applied to the implant material in the form of a sheet

(layer) to promote adherence to the tissue surfaces (column 5, lines 24-30). The applicant claims a thickness of 1 to 50 microns. Wironen does not teach the thickness of the chitosan layer.

With a reasonable expectation of successful results, it would have been obvious to one having ordinary skill in the art at the time of the invention to adjust the thickness for the chitosan layer to ensure that a sufficient amount of the adhesive layer was present to holds the implant in the desired position, without slippage, to better ensure long-lasting results (column 5, lines 58-62).

21. **Regarding 5**, Wironen teaches a biocompatible (Column 5, lines 43-45) coating (called by the term "a carrier", Column 4, lines 14-20) system for metallic implants (Column 4, lines 30-35). The carrier (coating) material is selected from or may be a combination of materials selected from the following non-exclusive list: collagen; gelatin; carboxymethyl cellulose; hyaluronic acid; polyvinyl alcohol; thrombin; fibrin; albumin; and mucoadhesive polysaccharides such as chitosan, polyalcohols, polyamines, polyvinyls, polyamides and polyesters (Column 5, lines 9-17). The applicant teaches a total weight of polysaccharide of not more than 50% weight.

Wironen also teaches that a coating where gelatin is used in the amount of 1-70% weight and preferably 25 to 40% weight (column 6, lines 10-12).

As both gelatin and chitosan are listed by Wironen as materials that can be used for coating materials, these materials are considered as functional equivalent materials with similar properties and would thus be readily exchangeable.

The applicant teaches a chitosan range of less than 50%. The weight range taught by Wironen covers the entire range taught by the applicant and the preferred range is within the scope of that taught by the applicant.

Wironen and the claim differ in that Wironen does not teach the exact same proportions as recited in the instant claim.

However, one of ordinary skill in the art at the time the invention would have considered the invention to have been obvious because the compositional proportions taught by Wironen overlap the instantly claimed proportions and therefore are considered to establish a prima facie case of obviousness. It would have been obvious to one of ordinary skill in the art to select any portion of the disclosed ranges including the instantly claimed ranges from the ranges disclosed in the prior art reference, absent unexpected results.

22. **Regarding Claims 6 and 7**, Wironen teaches a biocompatible (Column 5, lines 43-45) coating (called by the term "a carrier", Column 4, lines 14-20) system for metallic implants (Column 4, lines 30-35). The carrier (coating) material is selected from or may be a combination of materials selected from the following non-exclusive list: collagen; gelatin; carboxymethyl cellulose; hyaluronic acid; polyvinyl alcohol; thrombin; fibrin; albumin; and mucoadhesive polysaccharides such as chitosan, polyalcohols, polyamines, polyvinyls, polyamides and polyesters (Column 5, lines 9-17). Wironen does not teach an average molecular weight of the hyaluronic acid or hyaluronic acid

derivative between 300,000 and 500,000 Dalton or between 380,000 and 420,000 Dalton at claimed by the applicant.

With the reasonable expectation of success, a person of ordinary skills in the art at the time of the invention through routine experimentation would adjust the molecular weight of hyaluronic acid or its derivatives based on the amount of durability required for that component. Hyaluronic acid or its derivatives with higher molecular weights would be expected to be more durable than hyaluronic species with lower molecular weights. The determination of the appropriate average molecular weight would overlap with the ranges taught by the applicant in the course of optimization.

23. **Regarding Claims 9 and 11,** Wironen does not teach that the internal area of the polysaccharide layer is not degradable, at least completely within two years or the external polysaccharide layer is degradable with in 100 days as claimed by the applicant.

Collombel teaches the usage of chitosan in a biomaterial application where the speed of enzymatic degradation of chitosan is a function both of its molecular weight and its degree of acetylation (Column 5, lines 64-66).

Kuo discloses that the literature describes a number of approaches to modifying hyaluronic acid to reduce (control) the diffusivity (degradation) in vivo one of which includes the use of crosslinking agents (column 2, lines 19-23). Some crosslinking agents include formaldehyde, divinyl sulfone and bis-epoxides (column 3, lines 24-42) and carbodiimide (column 3, line 15-17). Kuo also discloses that by choosing the

concentration of hyaluronic acid one can control the rate of degradation or diffusion (column 12, lines 43-44).

Whereas, Wironen teaches a biocompatible coating for metallic implants which can be composed of hyaluronic acid and chitosan. Collombel and Kuo teach that both hyaluronic acid and chitosan can be selected with the appropriate structural features (crosslinking in hyaluronic acid and acetylation in chitosan) to control the degree of degradation.

It would have been obvious to some of ordinary skill in the art at the time of the invention to combine the biocompatible hyaluronic acid and chitosan coating metallic implant coating taught by Wironen with the suitable structural features (crosslinking in hyaluronic acid and acetylation in chitosan) taught by Kuo and Collombel to give the desired degradation properties in the respective layers to improve tissue compatibility and decrease the likelihood of infection.

24. **Regarding Claims 10 and 12,** Wironen, Collombel and Kuo do not teach an internal of polysaccharide layer thickness of 3 to 50 microns or an external thickness of 10 to 250 microns as claimed by the applicant.

With a reasonable expectation of successful results, it would have been obvious to one having ordinary skill in the art at the time of the invention to adjust the internal and the external thicknesses for the polysaccharide layers through routine experimentation of implant coating levels to determine the appropriate amount which would include the ranges claimed by the applicant.

25. **Regarding Claims 13, 14, 16,** Wironen teaches a biocompatible (Column 5, lines 43-45) coating (called by the term "a carrier", Column 4, lines 14-20) system for metallic implants (Column 4, lines 30-35). The carrier (coating selected from or may be a combination of materials selected from the following non-exclusive list: collagen; gelatin; carboxymethyl cellulose; hyaluronic acid; polyvinyl alcohol; thrombin; fibrin; albumin; and mucoadhesive polysaccharides such as chitosan, polyalcohols, polyamines, polyvinyls, polyamides and polyesters (Column 5, lines 9-17). Wironen implies that one may select a material from the list shown above or a combination of materials which the examiner interrupts to include if desired layers using chitosan or hyaluronic acid or combination thereof.

Wironen, Collombel and Kuo do not teach a composition such the vivo degradation of the polysaccharide layer is slowed from the outside in the direction of the main body of the implant, an internal polysaccharide layer that degrades not more than 20% weight within two years or an external polysaccharide layer that degrades at least 50% by weight with in 100 days as claimed by the applicant.

Collombel teaches the usage of chitosan in a biomaterial application where the speed of enzymatic degradation of chitosan is a function both of its molecular weight and its degree of acetylation (Column 5, lines 64-66).

Kuo discloses that the literature describes a number of approaches to modifying hyaluronic acid to reduce (control) the diffusivity (degradation) in vivo one of which includes the use of crosslinking agents (column 2, lines 19-23). Some crosslinking

agents include formaldehyde, divinyl sulfone and bis-epoxides (column 3, lines 24-42) and carbodiimide (column 3, line 15-17). Kuo also discloses that by choosing the concentration of hyaluronic acid one can control the rate of degradation or diffusion (column 12, lines 43-44).

Whereas, Wironen teaches a biocompatible coating for implantable prosthesis which can be composed of hyaluronic acid and chitosan. Collombel and Kuo teach that both hyaluronic acid and chitosan can be selected with the appropriate structural features (crosslinking in hyaluronic acid and acetylation in chitosan) to control the degree of degradation.

It would have been obvious to some of ordinary skill in the art at the time of the invention to combine the biocompatible hyaluronic acid and chitosan implantable prosthesis coating taught by Wironen with the suitable structural features (concentration of crosslinked hyaluronic acid and acetylation in chitosan) taught by Kuo and Collombel to give the desired degradation properties in the respective layers.

The process would involve ensuring that through routine experimentation the materials in the external and internal regions have a sufficient molecular weight and a suitable level of acetylation with respect to the chitosan material based on the teachings of Collombel and the appropriate concentration of crosslinked hyaluronic acid based on the teachings of Kuo to achieve the desire degradation rate in the internal and external regions. Through such routine experimentation, a person of ordinary skill in the art at the time of the invention could achieve a degradation that is slowed from the outside direction of the main body of the implant, an internal polysaccharide layer that

degrades not more than 20% weight within two years or an external polysaccharide layer that degrades at least 50% by weight with in 100 days as claimed by the applicant.

26. **Regarding Claim 15, 17-19,** Wironen, Collombel and Kuo do not teach the thickness of the polysaccharide layer as be 3 to 50 microns for the internal layer, 10 to 250 microns for the external layer, 10 to 400 microns or 50-120 microns in thickness.

With *a* reasonable expectation of successful results, *it* would have been obvious to one having ordinary skill in the art at the time of the invention to adjust the internal and the external thicknesses for the polysaccharide layers with respect to the desired degradation rate through routine experimentation of implant coating levels to determine the appropriate amount which would include the ranges claimed by the applicant. In the course of determining the optimal thickness the ranges covered by the applicant would be in scope, absence unexpected results.

27. **Regarding Claim 20**, Wironen, Collombel and Kuo teach the invention of claim 8. Wironen teaches a biocompatible (Column 5, lines 43-45) coating (called by the term "a carrier", Column 4, lines 14-20) system for metallic implants (Column 4, lines *30-35).* The carrier coating is selected from or may be a combination of materials which include hyaluronic acid and chitosan (Column 5, lines 9-17).

28. **Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wironen (6,685,626)/Collombel (5,166,187) in view of Kuo (US 6,537,979) and Swan (5,563,056).**

29. **Regarding Claim 21**, Wironen, Collombel and Kuo do not teach the polysaccharide layer is immobilized covalently or through physisorption on the surface of the implant.

Swan teaches a chemical specie can be immobilized in a three dimensional, crosslinked matrix by bringing together in covalent bonding proximity a desired chemical specie and a polymeric coupling compound such as a photoderivatized polymer having at least two latent photochemical reactive groups per molecule, each latent reactive group being capable when activated of covalently bonding to another coupling compound molecule or to the chemical specie (abstract).

Swan also teaches such materials which are readily coupled (immobilized) to a surface include oligomers, homopolymers and copolymers resulting from addition or condensation polymerization, and natural polymers including nucleic acids, oligosaccharides, linear polysaccharides such as amylose, dextran, chitosan, heparin and hyaluronic acid, and branched polysaccharides such as amylopectin, glycogen and hemi-celluloses (Column 3, lines 54-63). Swan also teaches that the immobilization of chemical species (on the surfaces of prostheses that are to be implanted within the body) with growth factors or similar chemical species may contribute to the rapid

proliferation of tissue (biocompatibility/ tissue growth) on the prosthesis (Column 1, lines 21-25).

Whereas both chitosan and hyaluronic acid homopolymers and copolymers can be immobilized on a surface covalently it would have been obvious to someone of ordinary skill in the art at the time of the invention to combine to biocompatible metallic implant coatings taught by Wironen with the immobilization technique taught by Swan to improve biocompatibility/ tissue growth, absent of unexpected results.

Response to Arguments/Amendments

The applicant argues that there is not motivation to combine the Kuo reference with Elliot and Wironen as Kuo teaches the use of hyaluronic acid to prevent tissue adhesion.

The examiner counters that one of ordinary skill at the time of the invention would look to the prior art for methods to control the degradation rate of hyaluronic acid which would have included the teachings of Kuo.

Kuo discloses a number of approaches to modifying hyaluronic acid to reduce (control) the diffusivity (degradation) which includes the use of crosslinking agents (column 2, lines 19-23). Kuo also discloses that by choosing the concentration of hyaluronic acid one can control the rate of degradation or diffusion (column 12, lines 43-44).

The motivation for combining the references would have been to utilize known techniques to control the degradation rate hyaluronic acid improve compatibility with surrounding tissue and decrease the likelihood of infection.

The applicant argues that Collombel does not teach or suggest a coating for an implant having a metallic body.

While Collombel does not mention chitosan being used as a coating for metallic prosthesis, Elliot clearly does mention it. One would have been motivated to look across the literature for ways to improve the biocompatibility of chitosan and the coating disclosed by Elliot is one such method.

The applicant argues that there is no motivation to look across the literature to improve the compatibility of chitosan.

The examiner counters that achieving improved biocompatibility of a material used to cover an implant would be a common desire as a means to reduce the likelihood of infection. This would have been ample motivation to look for approaches to improve compatibility and the approaches would have included those disclosed by Kuo and Collombel.

The applicant argues that degradation of the polymer component used by Elliot would be undesirable and lead to failure of the prosthesis.

The examiner counters that Elliot teaches an implantable stent made of a metal, such as stainless steel, tantalum, or niobium (paragraph 22). Elliot teaches that the skirt (outer covering the prosthesis) can be coated with materials that are susceptible to cell ingrowth (tissue simulating, biocompatible) (paragraph 25).

The combining of the reference would be concerned with improving the biocompatibility of the implant with respect to the surrounding tissue. The incorporation of control degradable materials is viewed as a means to decrease infection of the surrounding tissue and such an improvement would not promote failure of the prosthesis.

The applicant argues that the failure of the Elliot prosthesis would be worsened by the presence of a degradable coating and may lead to a hole in the prosthesis.

The examiner counters that the prosthesis of Elliot are made from metals. As stated earlier, the incorporation of control degradable materials is viewed as a means to decrease infection of the surrounding tissue and such an improvement would not promote failure of the prosthesis.

Elliot mentions in paragraph 6, a Type III failure is a mechanical failure, wherein a hole may be ripped into the prosthesis (e.g., excessive wear at a metal/non-metal (fabric or polymer) interface) or poor integrity exists at a connection, or connections, between modular components of a prosthesis.

Improved biocompatibility in metal/non-metal interface is viewed as a means to decrease the likelihood of poor integrity existing at a connection. It would thus, in an analogous sense, be desirable to use known approaches to improve biocompatibility of the surrounding tissue be incorporating known degradable materials at the metal/non-metal interface of a prosthesis to improve biocompatibility in the surrounding tissue.

The applicant argues that there is no motivation to combine Swan with Collombel and Kuo.

The examiner counters that Swan teaches that the immobilization of chemical species (on the surfaces of prostheses that are to be implanted within the body) with growth factors or similar chemical species may contribute to the rapid proliferation of tissue (biocompatibility/ tissue growth) on the prosthesis (Column 1, lines 21-25). This is viewed a means to decrease the likelihood of infection. Such as approach would be over interest to a person of ordinary skill in the art at the time of the invention.

The applicant argues that there is no motivation to improve the biocompatibility of chitosan and hyaluronic acid.

The examiner counters the each of the materials claimed by applicant was known at the time of the invention in the context of usage as a coating for metal implants. The general desire to improve biocompatibility would be viewed by one of ordinary skill are an obvious need in order to decrease the chances of infection. As the means to control the degradation of a coating layer was taught in the prior art, there would have been clear motivation to seek available means to improve the biocompatibility of chitosan and hyaluronic acid.

The applicant argues that the cited references do not teach the non-uniform degradation of the claimed coating.

The examiner counter that Elliot teaches the application of partial layers and Collombel/Kuo teaches the means to control degradation of a polysaccharide layer. It would have been obvious to a person of ordinary skill in the art at the time of the invention to have adjusted the acetylation of chitosan or the modification of hyaluronic acid with crosslinking agents to achieve a desirable degradation in a given layer which

would have included layers have different degradation rates (non-uniform), absent unexpected results.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGORY CLARK whose telephone number is (571)270-7087. The examiner can normally be reached on M-Th 7:00 AM to 5 PM Alternating Fri 7:30 AM to 4 PM and Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Tarazano can be reached on (571) 272-1515. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. Lawrence Tarazano/
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GREGORY CLARK/GDC/
Examiner
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